72. (New) The isolated nucleic acid molecule of claim 71 wherein the heterologous sequence is fused to the 5' terminus of said molecule.

73. (New) The isolated nucleic acid molecule of claim 71 wherein the heterologous sequence is fused to the 3' terminus of said molecule.

74. (New) The isolated nucleic acid molecule of claim 71 wherein the heterologous sequence is a nucleic acid encoding a polypeptide selected from the group consisting of polypeptides comprising:

a) pre- and pro- sequences that facilitate the transport, translocation and/or processing of the OMP21-derived polypeptide in a host cell;

b) affinity purification sequences; and

c) sequences that comprise one or more immunogenic epitope(s) of a surface exposed protein of a microbial pathogen.

75. (New) A recombinant expression vector comprising the nucleic acid molecule of claim 71.

76. (New) A host cell transformed with the expression vector of claim 75.

77. (New) A host cell transformed with the expression vector of claim 20.

78. (New) An isolated nucleic acid molecule encoding a fragment of an OMP21 protein, said fragment comprising at least 10 amino acids and having an antigenic epitope of the amino acid sequence of SEQ ID NO: 7.

REMARKS

The specification has been amended to delete the page numbers, etc. in the Table of Contents as such page numbers may not be appropriate for a granted patent. In addition, the specification has been amended at pages 25 and 39 to correct inadvertent editorial or typographical errors and at page 66 to insert the accession number provided by

the ATCC for the deposited microorganism. No new matter is added by any of these amendments.

Upon entry of the present amendments, claims 9, 11-13, 16, 20 and new claims 71-78 will be pending and under active consideration. Claim 9 has been amended to be independent and to incorporate the recitations of withdrawn claims 1 (on which it was dependent) and 2 and canceled claim 10. Claims 11-13, 16 and 20 have been amended and new claims 71-78 have been added to more clearly and distinctly define certain embodiments of the invention. Amended claims 9, 11-13, 16, and 20 are fully supported by the specification and the claims as originally filed. Specific support for claim 9 can be found, *e.g.*, in original claims 1 and 2. Support for the recitation of the specific apparent molecular weight of the molecular weight standards recited in the claim can be found in the description of Figure 2, at page 12, lines 3-21. Specific support for claim 13 can be found, *e.g.*, at page 45, line 11 through page 46, line 11; support for claims 20 and new claims 75-77 can be found, *e.g.*, at page 46, line 17 through page 50, line 18; support for new claims 71-74 can be found, *e.g.*, on page 19, lines 14-17; support for claim 78 can be found in the specification at page 4, line 24 through page 5, line 3 and at page 16, line 27 through page 17, line 14, particularly at page 16, line 31, and at page 19, lines 28-33. With the exception of the amendment of claim 9 to delete the phrase "a sequence substantially homologous thereto", the sum of the amendments are not narrowing amendments as they only more clearly delineate the originally claimed embodiments of the invention and do not change the overall scope of the original claims. No new matter has been added.

1. REJECTION OF CLAIMS UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

Claims 9-17, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph. While the Office Action admits that the specification is enabling "for an isolated nucleic acid molecule comprising a nucleic acid selected from the group consisting of: a) the nucleic acid as set forth in SEQ ID NO:2-6 and 8-20 or a complementary sequence thereof; b) a nucleic acid sequence encoding the polypeptide of SEQ ID NO:1 or 7 or a complementary sequence thereof", it alleges that the specification "does not reasonably provide enablement for using any nucleic acid which is 'substantially homologous to' OMP21 or a 'fragment' thereof or sequences which hybridize under stringent conditions".

It is further alleged that "because of the broad claim language regarding the hybridization conditions and the phrase 'a sequence substantially homologous thereto or any fragment thereof' numerous nucleic acid sequences which hybridize to the nucleic acids of applicants' invention but do not detect the presence of M. *catarrhalis* are encompassed by the claims. Essentially any nucleic acid which shares one base pair in common would hybridize under 'stringent conditions to the nucleic acid sequences claims.'"

Applicants respectfully disagree and traverse the rejection for the following reasons.

With regard to sequences substantially homologous to OMP21, merely in order to expedite prosecution of this application and not to acquiesce with the Examiner's rejection, the claims have been amended to further clarify Applicants' invention. The claims as presently amended do not recite the term "sequence substantially homologous to". Rather claim 11, as amended, in subsection "d" indicates that the nucleic acid sequence encoding OMP21 is "at least 70% identical to the sequence" of SEQ ID NO. 6, and further specifies that said sequence encodes "a polypeptide that elicits an immune response when administered to an animal." As clearly indicated in the specification in Section 5.7 which describes particular nucleic acids encoding "OMP 21", at page 39, lines 25-30, the term "substantially homologous" with respect to a nucleic acid sequence is defined to mean "at least 70%. . . identical to a reference sequence of identical size" using a search algorithm known in the art. Thus, although the claim does not recite the terminology, "sequence substantially homologous", it does recite the specific definition given that term in the specification. Subsection "d" further specifies that the encoded polypeptide elicits an immune response to *Moraxella*. This is completely consistent with the teaching of the specification, *e.g.*, in the Summary, in sections 5.1 and 5.2, etc.

With regard to nucleic acids encoding a fragment of OMP21, new claim 78 specifies "nucleic acid molecule encoding a fragment of an OMP21 protein, said fragment comprising at least 10 amino acids and having an antigenic epitope of the amino acid sequence of SEQ ID NO: 7". Attention is directed to the teaching of the present specification at page 4, line 24 through page 5, line 3 and at page 16, line 27 through page 17, line 14, particularly at page 16, line 31, and at page 19, lines 28-33. As clearly taught therein, nucleic acids encoding fragments of OMP21 as presently claimed are fully taught and enabled by the specification.

The office action further states that the only use taught for the claimed nucleic acid molecules is to detect *M. catarrhalis*. Applicants respectfully disagree. The claimed nucleic

acids, vectors comprising the nucleic acids, and host cells transformed with the vectors are indeed useful in detecting the *M. catarrhalis*, but the specification clearly teaches that the nucleic acids can be used in vaccine compositions as well as to produce OMP21 and OMP21 derived polypeptides (see *e.g.*, page 5, line 31 through page 6, line 7; page 21, lines 3-5; page 46, lines 14-26). The specification additionally teaches that the OMP21 polypeptides and the nucleic acids that encode them can be used as reagents for clinical/medical diagnosis of *M. catarrhalis* infections or for scientific research studying pathogenicity, virulence and infectivity of *M. catarrhalis* (page 50, lines 21-27). In addition, the specification teaches that OMP21 of the invention may also be used to prepare polyclonal and monoclonal antibodies that can be used to further purify compositions containing polypeptides of the invention by techniques well known to a skilled artisan. These antibodies may also be used as a screening tool for presence of antibodies to *M. catarrhalis* in a sample; as cytotoxic agents in passive immunizations and active ingredients in pharmaceutical compositions including vaccines (page 50, line 33 through page 51, line 6). Thus, the allegation that the only disclosed use of the nucleic acid molecules is to detect *M. catarrhalis* is not correct.

The Office Action specifically asserts that "(T)he specification does not teach how to adapt a vector for transformation of a host cell or for delivery of a sequence". In order to expedite prosecution of the present application, and not to acquiesce with this assertion, claims 13, 16, 20 and new claims 75-77 have been amended (or added) to further clarify Applicants' invention. The claims as presently amended do not recite the term "adapted for transformation of a host cell".

Further, it is noted that claims 13, 16, 20 and new claims 75-77 as amended, are directed to compositions comprising nucleic acids that encode full length OMP21 or sequences complementary to said nucleic acids. The claimed vectors and host cells must comprise the nucleic acids recited in the claims but may also comprise additional residues. For instance, vectors and host cells comprising SEQ ID NO:12 must also comprise additional nucleic acids to encode a 16 to 20 kD OMP21 protein. Therefore the claimed nucleic acids, vectors and host cells have use in the production of OMP21 protein. The specification, *e.g.*, at Section 5.8, at pages 46-50 clearly provides more than ample guidance to enable one of skill in the art to practice the claimed invention.

It is alleged that the specification does not enable one of skill to determine which "expression means" are useful in the invention and that is unclear whether the term refers to a

promoter sequence, a nucleic sequence, a nucleic acid sequence which expresses a protein or some other compound. Applicants respectfully disagree. However, merely in order to expedite prosecution, the claims as amended do not recite the term "expression means".

Attorneys for Applicants point out that claim 20, as amended, and new claim 75 are directed to a "recombinant expression vector". Claim 20, in particular recites that the recombinant expression vector comprises the nucleic acid molecule of claim 9, 11 or of the plasmid of claim 12 "operably linked to a nucleic acid for transcription and translation of said nucleic acid molecule encoding the OMP21 protein". The specification *e.g.*, at page 46, line 14 through page 49, line 32 discloses expression vectors which contain the necessary elements for transcription and translation of the inserted polypeptide encoding sequence(s) which comprise the nucleic acid molecule(s) of claim 9, 11, or the plasmid of claim 12. It is well known to those skilled in the art of molecular biology what elements are necessary for transcription and translation of a nucleic acid encoding a protein, including but not limited to promoter/enhancer elements, replication site, sequences which are capable of providing phenotype selection (i.e. ampicillin or tetracycline resistance) and replicon and control sequences that can be used to transform host cells. See also the detailed teaching of the present specification at page 47, lines 25-29 and 33-36; page 48, line 20 through page 49, line 8; and page 60, lines 16-18.

It is also alleged that the specification does not teach "leader sequences" for secretion or purification. Applicants respectfully disagree. There is no need to specifically teach the term "leader sequence" since it is well known to those skilled in the art. "(A) patent need not teach, and preferably omits what is well known in the art". *Hybritech Inc., v Monoclonal Antibodies, Inc.*, 802 F 2d 1367, 231 USPQ 81 (Fed. Cir. 1986). However, merely in order to expedite prosecution, the claims as amended do not recite "leader sequences". Instead, claim 71 recites an "isolated nucleic acid molecule of claim 9 or 11 further comprising a heterologous sequence". Claims 72-73 recite, respectively, that the heterologous sequence is fused at the 5' and the 3' terminus of the OMP21 encoding molecule. Claims 71-73 are fully enabled by the teaching of the specification at page 19, lines 13-24. Claim 74 recites that the heterologous sequence is selected from sequences encoding polypeptides that "facilitate the transport, translocation and/or processing of the OMP21-derived polypeptide", "affinity purification sequences" and "any useful immunogenic sequences (*e.g.*, sequences encoding one or more epitopes of a surface exposed protein of a microbial pathogen)"(see page 19,

lines 13-24 for a detailed teaching in the specification). Claim 74 is fully enabled by the specification at page 19, lines 13-24. With respect to the term "affinity purification sequences", attention is directed to Exhibit C attached hereto. Exhibit C is a part of ch.16 of a general text of "protocols" for molecular biology which convincingly demonstrates that, at the time the application was filed, one skilled in the art would understand and be able, without undue experimentation, to use nucleic acids encoding an affinity purification sequence as a heterologous sequence with a sequence encoding a desired protein.

It is alleged that "the specification does not enable transforming of host *cells in vivo* encompassed by claims 16 and 17 or delivery to a host in *vivo* (claims 20 and 21)." In support of this assertion, Verma *et al.* (Nature, Vol. 389, pages 239, 1997) is cited. Applicants respectfully disagree for the following reasons. Verma *et al.* states that the problem with using *in vivo* transformation techniques with respect to gene therapy is an inability to sustain gene expression. The present claims are directed to nucleic acids that encode OMP21 polypeptides. The compositions can be used *in vitro* or *in vivo*. When used *in vivo,* the nucleic acids are used for therapeutic and prophylactic purposes by way of a vaccine that will stimulate anti-OMP21 immune response, *e.g.*, antibody production. The state of the art regarding *in vivo* transformation of host cells for the purposes cited in the specification was within the realm of routine experimentation for one of skill in the art at the time of the invention. Applicants provide herewith as evidence a list of five references shown in Exhibit B. A copy of each of these references, designated References AL-AP is submitted with the Supplemental Information Disclosure Statement. This list is certainly not exhaustive, but is provided to exemplify the realm of literature available at the time of filing of the instant specification. Contrary to the assertions in the Office Action that the specification does not disclose transforming cells *in vivo* or delivering the sequences to a host *in vivo*, the specification on pages 5, lines 4-9 and page 26, lines 16-19; page 29, line 27 through page 30, line 8; page 32, lines 4-9; page 51, lines 4-6 clearly discloses the use of the claimed nucleic acid molecules and vectors *in vivo*.

Therefore, in view of the above, one with skill in the art would be enabled, without undue experimentation, to make and use the claimed nucleic acid molecules, vectors and host cells and this rejection should be withdrawn.

2. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 9-17, 20 and 21 are rejected under 35 U.S.C. 112, second paragraph. Applicants respectfully traverse the rejections for the following reasons.

It is alleged that claims 9-11, 13-17, 20 and 21 are indefinite because it is unclear what applicants consider "substantially homologous". As explained above, merely, in order to expedite prosecution in the subject application and not to acquiesce with the Examiner's rejection, these claims have been amended to recite the definition of the term provided in the specification and as presently amended do not recite the term "substantially homologous".

It is alleged that claims 11, 13-17, 20 and 21 are indefinite because it is not clear what applicants consider "stringent conditions". In order to expedite prosecution in the subject application and not to acquiesce with the Examiner's rejection, these claims have been amended to further clarify Applicants' invention. The claims as presently amended recite the specific conditions intended by the term "stringent conditions".

The rejection of claim 12 is moot because Claim 12 has been amended to recite the accession number.

The rejection of claims 13, 14, 20 and 21 with respect to the term "adapted" as indefinite is moot because, in order to expedite prosecution in the subject application and not to acquiesce with the rejection, the claims have been amended to delete the term and/or cancelled without prejudice.

The rejection of claims 14, 15 and 21 as indefinite because it is unclear what "expression means" refers to is moot because, in order to expedite prosecution of this application, these claims have been canceled without prejudice and/or replaced by amended claims.

Further, it is also alleged that claim 15 is indefinite because it is not clear how a leader sequence correlates to secretion or purification. It is also alleged that the specification does not teach leader sequences for secretion or purification. Once again, this is a moot point since this claim has been canceled without prejudice.

The rejection of claims 16 and 17 as indefinite because of the use of term "containing" is moot in view of the amendment of claims 16 to substitute "comprising" for "containing"and the cancellation of claim 17.

The Office Actions' rejection of claim 14 as indefinite because of the use of the phrase "host of said OMP21" is moot in view of the fact that this claim has been cancelled without prejudice.

It is alleged that the use of the term "substantially purified" in original claim 1, incorporated into claim 9 is indefinite.

Applicants respectfully disagree. It is well established that "claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of specification in giving them their "broadest reasonable interpretation"". *In re Okuzawa*, 537 F 2d 545, 548, 190 USPQ 464, 466 (CCPA 1976). The specification on page 4, lines 17-23, teaches that OMP21 is at least 70 wt % pure, preferably at least 90% wt pure. In view of the teachings of the specification, one with skill in the art would understand that "substantially purified" means that the OMP21 constitutes at least 70% of the preparation. However, for the sake of expediting the application, the claim as amended does not include the term "substantially purified".

It is also alleged that the metes and bounds of proteins encompassed by the claim language cannot be determined due to the use of term "apparent molecular weight" or "about 16kD to 20 kD." Applicants respectfully disagree. The claims recite that the apparent molecular weight of OMP21 is "about 16 to about 20 kD as determined by SDS –PAGE" (emphasis added by Applicants). Further, the claims specify the apparent molecular weight of two molecular weight standards. This language would surely be understood by one skilled in the art. On *e.g.*, page 12, lines 3-21, Figure 2, page 14, lines 10-14 and page 16, lines 4-24 the specification discloses the methods used to determine apparent molecular weight (molecular weight estimation) in SDS-PAGE. One with skill in the art recognizes that determination of apparent molecular weight depends upon the particular conditions used to characterize the protein and/or due to use of different molecular weight markers.

In view of the above, this Section rejection should be withdrawn.

3. REJECTIONS UNDER 35 U.S.C. § 102

Claims 9-11, 13-17, 20 and 21 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by EP 0614 989 by Claus Krebber, (hereinafter "Krebber"). [1]It is alleged that

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[1] To further clarify the record, Applicants note that the first named inventor of (continued...)

Krebber teaches "a primer which has 100% homology to SEQ ID NO:16 from base pairs 3-27 (page 7, line 23, second primer)". Applicants respectfully disagree.

Firstly, residues 3-27 of the nucleic acid molecule taught by Krebber have sequence identity only to residues 4-28 of SEQ ID NO:16 of the present application. SEQ ID NO:16 contains 45 nucleotides and therefore, the sequence taught by Krebber is at most only 55.6% (25/45) (identical) homologous to the nucleotide sequence identified as SEQ ID NO:16.

From reading Krebber, it would appear that the sequence taught by Krebber is a primer useful in amplifying and cloning gene III of bacteriophage M13 (see Krebber page 7, lines 16-31). The sequence taught by Krebber is not a complementary sequence to a nucleic acid encoding OMP21.

Further, the sequence taught by Krebber is not substantially homologous to a nucleic acid encoding OMP21 or even to SEQ ID NO:16 because the specification on page 39, line 23 through page 40, line 7 and page 15, line 1 through page 16, line 7 defines a "substantially homologous" sequence as one which is at least 70% identical to a reference sequence of identical size or when the alignment of comparison is by a computer homology program or search algorithm known in the art including, e.g., BLAST analysis disclosed on pages 15-16 of the specification. The sequence taught by Krebber is only at most 55.6% (25/45) identical to SEQ ID NO:16 and 4.6% (25/543) identical to SEQ ID NO:7 which encodes full length OMP21.

As originally claimed, claim 9, the broadest original claim to nucleic acid molecules, recited an isolated nucleic acid molecule encoding OMP21, a sequence complementary thereto, a sequence substantially homologous thereto, or a fragment thereof. For reasons detailed above, with the exception of "any fragment of said nucleic acid molecule", the cited sequence of Krebber does not anticipate any of the subject matter of original claim 9.

With respect to independent claims 9 and 11, as presently amended, which recite a nucleic acid molecule encoding a 16 to 20 kD OMP21 protein or a sequence complementary to a sequence encoding such a protein, the sequence taught by Krebber can not encode a 16 to 20 kD OMP21 protein since it can encode at most 14 amino acids, and thus the cited Krebber sequence cannot and does not anticipate such molecule.

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[1] (...continued)
EP 0614 989 is Claus Krebber and not Krebber Claus.

With respect to independent claim 78 which recites a nucleic acid molecule encoding a fragment of an OMP21 protein, this claim, as amended, is directed to a preferred fragment which comprises at least 10 amino acids and has an antigenic epitope of the amino acid sequence of SEQ ID NO:7. Accordingly, the molecule of Krebber, which at most encodes 8 amino acids identical to a small portion of OMP21, does not and cannot encode a fragment of OMP21 as presently claimed.

For the foregoing reasons, the nucleic acid molecule taught by Krebber does not anticipate the claimed invention and the rejection must be removed.

Claims 9-11, 13-17, 20 and 21 are rejected unde35 U.S.C. 102(b) as being anticipated by Darrasse et al WO93/25708 (hereinafter "Darrasse"). Darrasse is alleged to teach on page 33, line 21 "a primer with 93.3% homology to base pairs 13-27 [sic] of SEQ ID NO:12". Applicants respectfully disagree.

From reading the English translation of the abstract of page 1 of Darrasse (in French), it appears that Darrasse pertains to nucleic acids encoding pectate-lyase of the bacterial genus Erwinia . In order to clarify the record, it is noted that the sequence taught by Darrasse can not have 93.3% homology to base pairs 13-27 of SEQ ID NO:12 since SEQ ID NO:12 is only 18 nucleotides in length. Moreover, even if the rejection were based on the assertion that nucleotides 13-27 of the cited Darrasse sequence (having 30 nucleotides) were 93.3% identical to nucleotides 1-18 of SEQ ID NO:12, the rejection must fail because, as originally claimed, all the nucleic acid molecules of the present invention encode an OMP21 protein of 16 to 20 kD, or comprise a complement thereof, a sequence substantially homologous to the nucleic acid encoding OMP21, or a sequence encoding a fragment of OMP21, wherein the smallest fragment described in the specification has at least 6 amino acids. None of such subject matter is disclosed in Darrasse, not even a fragment because the cited sequence is not 100% homologous, only 93.3% identical to a sequence encoding 6 amino acids. Further, as discussed above, with regard to independent claims 9 and 11, Applicants have amended the claims to more particularly and distinctly claim certain embodiments of their invention. The claims have been amended to recite a nucleic acid encoding a 16 to 20 kD OMP21 protein, or a sequence complementary to such nucleic acid. The reference does not teach or enable the subject matter of the claims as presently amended. Independent claim 78 claims a nucleic acid encoding a fragment of OMP21 having at least 10 amino acids. Such molecule is not

disclosed by Darrasse which, at most, discloses a molecule 93.3% identical to a nucleic acid molecule encoding only 6 amino acids.

For the foregoing reasons, the nucleic acid molecule taught by Darrasse does not anticipate the claimed invention and the rejection should be removed.

Claims 9-11, 13-17, 20 and 21 are rejected under 35 U.S.C. 102 (e) as being anticipated by Wadsworth, et al., US patent 5,604,141 (hereinafter "Wadsworth"). It is alleged that Wadsworth teaches a primer, in column 45, denoted SEQ ID NO:16, with 93.8% homology to base pairs 33-48 of SEQ ID NO:13 of the present application.

Applicants respectfully disagree. In order to clarify the record, it is noted that the sequence taught by Wadsworth can not have 93.8 % homology to base pairs 33-48 of SEQ ID NO:13 of the present application since SEQ ID NO:13 is only 18 nucleotides in length. Moreover, even if the rejection were based on the assertion that nucleotides 33-48 of the cited Wadsworth sequence (having 90 nucleotides) were 93.8% identical to nucleotides 1-18 of SEQ ID NO:13, the rejection must fail essentially for the same reasons detailed above with respect to Darrasse. As originally claimed, this is true even for the nucleic acid encoding a fragment since the smallest nucleic acid molecule, as originally claimed, must encode at least 6 amino acids and the cited reference encoding only 6 amino acids, which are 93%, not 100% identical to a small portion of OMP21. Independent claim 78 claims a nucleic acid encoding a fragment of OMP21 having at least 10 amino acids. Such molecule is not disclosed by Wadsworth which, at most, discloses a molecule 93% identical to a nucleic acid molecule encoding only 6 amino acids.

Presently amended claims 9 and 11 recite a nucleic acid encoding a full length 16 to 20 kD OMP21 protein, or a sequence complementary to such nucleic acid. SEQ ID NO:16 of Wadsworth can not and does not encode a 16 to 20 kD OMP21 protein since it can encode at most 30 amino acids. SEQ ID NO:16 of Wadsworth is not a complementary sequence to a nucleic acid encoding OMP21.

For the foregoing reasons, the nucleic acid molecule taught by Wadsworth et al. does not anticipate the claimed invention and the rejection should be removed.

CONCLUSION

In light of the above amendments and remarks, attorneys for the Applicants submit that the claims are in condition for allowance. An early allowance is earnestly sought.

Respectfully submitted,

Date December 20, 2000

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Exhibit B
Attorney Docket No. 7969-074
U.S. Application Serial No. 09/164,714
List of References

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